REMARKS

Rejections under 35 U.S.C. §103:

I. Claims 15-18 and 23-27 stand rejected as allegedly obvious in view of the combined disclosures of Vallet Mas et al. (EP 0 717 989) and Redlich et al. (US 5,225,279).

II. Claims 19-20 stand rejected as allegedly obvious over the combined disclosures of Vallet Mas et al. and Weitschies et al. (US 6,068,857).

III. Claim 21 stands rejected as allegedly obvious over the combined disclosures of Vallet Mas et al. and Liversidge et al. (US 6,045,829).

When applying 35 U.S.C. § 103, the following tenets of patent law must be adhered to: (A) The claimed invention must be considered as a whole; (B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; (C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and (D) Reasonable expectation of success is the standard with which obviousness is determined.[1]

"To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings."[2] Indeed, "to support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references."[3] The examiner may not, because of doubt that the invention is patentable, resort to speculation, unfounded assumption or hindsight reconstruction to supply deficiencies in the factual basis for the rejection.[4] "Second, there must be a reasonable expectation of success."[5]

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[1] *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).
[2] MPEP §2143.
[3] *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985).
[4] *See In re Warner*, 379 F.2d 1011, 1017, 154 USPQ 173, 177 (CCPA 1967), *cert. denied*, Appeal No. 2002-1187 389 U.S. 1057 (1968).
[5] MPEP §2143. See also: *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1354 (Fed. Cir. 2003).

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure.[6] That it would have been obvious to try is not sufficient.[7] "Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations."[8]

In view of the above principles, the rejection of claims 15-18 and 23-27 as allegedly obvious in view Vallet Mas et al. and Redlich et al. does not establish a *prima facie* case of obviousness with regard to the invention of claim 15 as a whole, or with regard to the invention of claim 26 as a whole.

Claim 15 requires that "an X-ray amorphous active ingredient is present in the core together with one or more copolymers of acrylates, methacrylates, methacrylic acid or acrylic acid, and the shell consists of a stabilizing coating matrix."

Claim 26 requires "an X-ray amorphous active ingredient is present in the core together with one or more polymers selected from the group consisting of copolymers of acrylates, methacrylates, methacrylic acid and acrylic acid."

Neither Vallet Mas et al. nor Redlich et al. teach the production of a nanoparticulate preparation where the active ingredient is present in the core in an X-ray amorphous state. The claims require this feature, and the specification stresses its importance, stating:

> The active ingredient in the interior of this core is present in X-ray amorphous form. It is essential that no crystalline active ingredient fractions are detectable (X-ray diffraction) in the active ingredient preparation. In particular, the polymers in the interior of the particles contribute to maintaining the active ingredient in its noncrystalline state and to stabilizing the colloidal structures in relation to homogeneous particle growth (Ostwald ripening).[9]

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[6] *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).
[7] Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1380 (Fed. Cir. 1986).
[8] MPEP §2143.
[9] Page 4, indicated lines 3 – 10 of the present Specification.

According to the process as disclosed in Vallet Mas et al. a first phase containing either droplets or solid particles emulsified or dispersed in a solvent, wherein the solid particles can have the active ingredient dispersed inside, is mixed with a second phase, which is a solution of a coating polymer in a solvent miscible with the solvent of the first phase. According to page 3, lines 37 – 43, Vallet Mas et al. specifically seek to avoid the immediate deposition of the polymer when the 2 phases come in contact in the mixing zone. The coating is only deposited on the droplets/particles when the solvent is later evaporated, i.e. during pulverization or nebulization. The active ingredient is either dissolved in a lipidic phase as a nanoemulsion. Vallet Mas et al. provide no teaching or suggestion that the particles of the first phase can contain the active ingredient in the X-ray amorphous state.

According to Redlich et al. a core emulsion containing acrylate monomers, carboxylic acrylate monomers, and optionally an active ingredient is heated to initiate polymerization. Subsequently at least one base is added to the dispersion, thereby neutralizing the polymerized carboxylic acid and developing the core/shell structure of the particles (see col. 5, lines 50-65). The core comprises the active in paraffine or other mineral solvents see for instance ex. B or C. Redlich et al. are completely quiet on the state of the active ingredient, and therefore provide no teaching or suggestion that the particles contain the active ingredient in an X-ray amorphous state. Moreover, since Redlich et al. refer to core/shell particles which are obtained by a different process, the particles would have a different structure.

A skilled artisan would not be motivated to introduce acrylic polymers known from Redlich et al. into core/shell particles as known from Vallet Mas et al., since the core/shell structure of Redlich et al. is formed with only one polymer and not with different polymers for the core and for the coating as in Vallet Mas et al. Moreover, Vallet Mas et al. only disclose the use of polymers as shells, not as part of a core that contains an X-ray amorphous active ingredient <u>together</u> with one or more polymers. The examiner argues that "[a] skilled artisan would be motivated to find improved polymers in order to incorporate a wider variety of active agents."[10] Without the benefit of hindsight, a skilled artisan would have needed more than a motivation to find improved

[10] Page 3, lines 10 – 11 of the present Office action.

polymers. A skilled artisan would have needed a teaching, suggestion, or motivation to modify the structure disclosed by Vallet Mas et al., i.e., to modify a core that contained no polymers to a core that contained an X-ray amorphous active ingredient together with one or more polymers.

Furthermore, with regard to claim 15, the X-ray amorphous state is achieved because the claimed process also requires "... mixing an active ingredient/polymer solution or precipitate with an aqueous solution of a polymeric coating material continuously in a mixing chamber by spraying the two components as a compact jet into a mixing chamber...."[11] Upon mixing the phase containing the active ingredient with the aqueous solution of the coating polymer, a dispersion containing the precipitated core/shell particles is formed. Neither Vallet Mas et al. nor Redlich et al. teach or suggest such a process step.

It is respectfully submitted that Vallet Mas et al. and Redlich et al. cannot be combined to establish a *prima facie* case of obviousness with regard to the invention of claim 15 as a whole, or with regard to the invention of claim 26 as a whole. "If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious."[12] Thus, claims 16 – 21, and 23 – 25, which depend from claim 15, are unobvious. Similarly, claim 27, which depends from claim 26, is unobvious.

Claims 19 and 20 stand rejected over the combination of Vallet Mas et al. and Weitschies et al. (US 6068857). The Weitschies et al. reference has been cited for disclosing gelatin as shell material. However, a combination of the two teachings cannot lead to the claimed invention, since as discussed above, Vallet Mas et al. does not disclose a core having an X-ray amorphous active ingredient and Weitschies et al. refers to particles with a gaseous core phase.

Claim 21 stands rejected over the combination of Vallet Mas et al. and Liversidge et al. (US 6,045,829). The Liversidge et al. reference is relied upon regarding the use of caseinates as surface stabilizers in nanoparticle dispersions. Again, Vallet Mas et al. does not lead to particles with a core containing X-ray amorphous active

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[11] Claim 15.
[12] MPEP §2143.03, citing *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

ingredients. According to Liversidge et al., crystalline drug particles are surface stabilized with gelatin and the like. These teachings when taken in combination with the disclosure of the other references cannot lead the skilled person to the claimed invention.

Since a *prima facie* case of obviousness has not been established a showing of unexpected results is in no way required, however, as expressed in the specification:

> Surprisingly, the colloidal active ingredient preparations according to the invention show distinctly less growth of hydrosol particles than known active ingredient preparations which consist essentially exclusively of active ingredient mass in the core of the colloidal particles One hour after the aqueous hydrosols have been prepared in the presence of a solvent dissolving the active ingredient, the particle growth is a factor of 4 to 10 less In the case of aqueous hydrosols which contain no solvent dissolving the active ingredient, the particle growth is reduced by a factor of 1.5 - 5.[13]

It is noted that the examiner criticized applicant's declaration, however it is also noted that List et al. is no longer applied in a rejection. Any reflection on the examiner's remarks has been omitted as moot.

[13] Page 3, indicated lines 30 – 39 of the present Specification.